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Combination Therapy with Ampicillin and Daptomycin for Treatment of *Enterococcus faecalis* Endocarditis

Enterococci are identified as the causative pathogen in approximately 10 percent of infective endocarditis cases, and the most frequently isolated species are *Enterococcus faecalis* and *Enterococcus faecium* (3). Gentamicin in combination with penicillins or glycopeptides is recommended for enterococcal endocarditis treatment; however, the incidence of ototoxicity and nephrotoxicity with aminoglycosides is a concern, especially in older patients. Daptomycin is a cyclic lipopeptide with *in vitro* activity against a variety of Gram-positive pathogens, including *Enterococcus* spp., exhibiting a unique mechanism of action resulting in rapid bacterial cell death. However, development of resistance in enterococci with daptomycin monotherapy has been reported (1). *In vitro* combinations of daptomycin and ampicillin have demonstrated a delayed ability to select out strains of *Enterococcus* with MICs of >4 μg/ml after multiple serial passages (2). Sakoulas and colleagues reported a case of a hemodialysis patient with ampicillin- and vancomycin-resistant *E. faecium* left-sided endocarditis who failed on a combination of daptomycin (6 mg/kg of body weight every 48 h [q48h]) and linezolid. The patient then received a combination of daptomycin (12 mg/kg q48h) and ampicillin (1 g q6h), with blood cultures clearing within 24 h. Additional studies of this isolate demonstrated that ampicillin reduced the net positive bacterial surface charge for an increased bactericidal effect of daptomycin (4). While the published clinical data on the treatment of enterococcal endocarditis using a combination of daptomycin and ampicillin are scarce, we feel that daptomycin plus ampicillin is a reasonable treatment option for enterococcal endocarditis, have integrated this combination into our treatment armamentarium, and have treated several patients successfully.

We report a case of an 89-year-old Caucasian female in good health but with a history of chronic hypertension and stage 4 chronic kidney disease (estimated baseline glomerular filtration rate [GFR] of 25 ml/min) who was admitted to the hospital after developing fever, generalized weakness, confusion, and an episode of cholelithiasis 2 weeks prior to the current admission. Levofloxacin was started empirically, and blood cultures were obtained. On day 2 of admission, blood cultures grew *E. faecalis* susceptible to daptomycin (MIC ≤ 4 μg/ml) and ampicillin. A transesophageal echocardiogram revealed a 0.89- by 1.4-cm mitral valve vegetation. Her cardiologist determined she was not a candidate for surgery. An infectious disease consult led to a decision to manage the patient medically. Levofloxacin was discontinued, and ampicillin (1 g q6h) and daptomycin (6 mg/kg q48h) were initiated with a goal of 6 weeks of therapy. Creatine phosphokinase was measured routinely throughout the 6 weeks, with no significant elevation noted. At week 6, blood cultures were negative and antibiotics were stopped, and repeat blood cultures 2 weeks later were also negative. Twelve months later, the patient was alive and had no clinical signs of endocarditis or active infection.

The combination of daptomycin and ampicillin yielded a successful outcome for treating *E. faecalis* endocarditis in this patient while providing an alternative to daptomycin monotherapy or an aminoglycoside-containing regimen. It has been suggested that doses higher than those approved by the FDA should be used to treat staphylococcal bacteremia; however, as shown here, when using an FDA-approved dose in combination with ampicillin, increased doses may not be necessary. Additional studies are needed to further explore this combination for the treatment of enterococcal endocarditis.

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